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Ultra-Restrictive Transfusion Thresholds in Critically Ill Adults: Are We Ready for the Next Step?

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ABSTRACT

Anemia is almost universal in critically ill patients, with 25% receiving blood transfusions as clinicians aim to prevent insufficient oxygen delivery. The current 'restrictive' hemoglobin (Hb) threshold of 7 g/dL for the nonbleeding critically ill population is supported by several landmark transfusion trials. While some trials have investigated lower transfusion thresholds, these were not conducted in this specific population. Transfusion is associated with various risks including transfusion-associated circulatory overload, transfusion-related acute lung injury, and hemolytic reactions. Moreover, transfusion products are scarce and expensive as they are produced from voluntary blood donations. Therefore, it is essential to limit blood transfusion to when absolutely necessary. Research indicates that several patient categories tolerate lower Hb levels than 7 g/dL. For instance, studies on acute hemodilution in healthy volunteers have shown that lower Hb levels do not lead to organ ischemia. Similarly, studies involving patients who refuse transfusions, often report lower Hb levels down to 5g/dL or less. These lower Hb levels appear to have limited impact on mortality or morbidity related outcomes. In patients with severe burns or hematological disorders, Hb levels below 7 g/dL are not associated with significant adverse outcomes. These findings suggest that the transfusion threshold for critically ill patients could potentially be lowered, as Hb levels under 7 g/dL do not inherently lead to increased mortality or morbidity. An individualized approach to deciding whether to transfuse or not might be best. This shift in transfusion practice could help reduce costs and minimize the risks associated with blood transfusions.

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Introduction

Many patients in the intensive care unit (ICU) develop anemia. Anemia increases the risk of organ ischemia. It is therefore treated with red blood cell (RBC) transfusions with the aim to improve oxygen delivery (DO_2) and reduce the potential for organ ischemia. According to a recent international prospective cohort study, 25% of critically ill patients received 1 or more RBC transfusion during ICU admission with a median of 1 RBC unit per transfusion event [1].

However, transfusion can result in severe complications and has been associated with increased short- and long-term mortality [2,3]. Therefore, over the past 25 years, extensive research has been conducted to determine the optimal RBC transfusion threshold in various critically ill populations. This threshold needs to balance the potential advantage of increasing DO_2 and using the lowest number of transfusions as possible to prevent transfusion associated complications.

Hébert et al.[4] was the first to compare a restrictive hemoglobin (Hb) transfusion threshold (commonly defined as 7 g/dL) with a liberal Hb transfusion threshold (commonly defined as ± 9 g/dL) in nonbleeding critically ill patients. This study demonstrated that a restrictive transfusion policy was noninferior to a liberal transfusion policy. Since then, large randomized controlled trials in various patient groups have consistently shown that a restrictive transfusion policy for the nonbleeding critically ill population is safe. In subgroups including, but not limited to patients postcardiac surgery, septic shock, and even acute coronary

Abbreviations: AIHA, auto-immune hemolytic anemia; APACHE II, acute physiology and chronic health evaluation II; ATP, adenosine triphosphate; DO_2, oxygen delivery; EPO, erythropoietin; ESICM, European Society of Intensive Care Medicine; Hb, hemoglobin; Hb S, sickle hemoglobin; HTRs, hemolytic transfusion reactions; ICU, intensive care unit; IQR, inter quartile range; OR, odds ratio; RBC, red blood cell; SD, standard deviation; SE, standard error; SEM, standard error of the mean; TACO, transfusion associated circulatory overload; TRALI, transfusion relate acute lung injury; TRIM, transfusion related immunomodulation.

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syndrome, a restrictive transfusion policy is proven to be noninferior [5–9]. For patients with acute brain injury, results are conflicting [9,10]. Consequently, 7.0 g/dL has become the standard transfusion threshold for various patient groups [11].

However, the rationale for selecting a lower transfusion threshold of 7.0 g/dL in the critically ill population remains unaddressed. While some studies have investigated lower thresholds, they focused on different patient groups, such as obstetric [12,13] and orthopedic trauma patients [14]. Furthermore, increasing evidence suggests that lowering the threshold to 5g/dL could be safe, as shown in studies on acute hemodilution and various patient groups [15–19]. Besides the risks associated with transfusions, blood products are expensive and often limited in availability. Further lowering the transfusion threshold could address these problems.

In this critical analytic review, we will describe oxygen transport through the body, the body's compensatory mechanisms for anemia and the risks of transfusion. We will then address studies investigating critical Hb levels, followed by an overview of patient populations where transfusion thresholds lower than the current Hb value of 7 g/dL are increasingly applied. Finally, we will discuss future perspectives in the research surrounding RBC transfusion thresholds.

Background

Oxygen Transport and Utilization

All cells in our body are dependent on oxygen for survival. It is used by mitochondria to oxidize nutrients which results in production of adenosine triphosphate (ATP) [20]. In the lungs oxygen diffuses over the alveolar membrane to the blood after which 99,9% of oxygen transport occurs through the binding of oxygen to Hb. Oxygen delivery to the tissue in milliliters per minute is termed DO_2 (Figure 1) and depends on 3 key parameters: cardiac output made up of heart rate and stroke volume, plasma Hb concentration and Hb oxygen saturation. A fall of either of these 3 key parameters can result in a critical decrease in DO_2. When DO_2 falls below a certain threshold, cell metabolism becomes impaired which ultimately manifests with systemic symptoms such as elevated lactate levels and signs of organ failure indicating insufficient oxygen delivery (e.g. altered consciousness, electrocardiogram changes, decreased urine production) [20].

The organs with the highest metabolic demand, namely the heart and the brain, receive a greater proportion of blood flow and thereby greater oxygen delivery [21,22]. In anemia, the body employs a range of physiological compensatory mechanisms to maintain DO_2. Coronary arteries dilate, which concomitant increased coronary blood flow boosting cardiac output [23]. Given a constant systemic oxygen use, this requires that some organs, such as the gut or the kidney, must reduce their oxygen consumption.

In peripheral tissues, enhanced oxygen extraction is achieved through modulation of microvascular blood flow. There, anaerobic ATP production results in acidosis, which decreases oxygen affinity of Hb hereby enabling oxygen release. All these compensatory processes result in a decrease in venous oxygen content while maintaining stable tissue oxygen concentration.

However, if Hb drops below a certain critical level, despite all these compensatory mechanisms and in the absence of hypoxemia, sufficient DO_2 can no longer be maintained. In this setting, RBC transfusion is considered essential to improve oxygen delivery. If the inadequate tissue perfusion remains untreated, this will ultimately progress to organ ischemia.

In current clinical practice, a single Hb value < 7g/dL is used as a transfusion trigger, even though there is limited correlation between Hb levels and actual insufficient DO_2 [24]. Nevertheless, at this moment there are no clinically available assays that predicted insufficient DO_2.

Risks of Red Blood Cell Transfusion

Over the past 20 years, evidence has increasingly shown that blood transfusions carry potentially life-threatening complications. The primary causes of severe transfusion-associated morbidity and mortality are transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) with febrile nonhaemolytic transfusion reaction being most frequently observed [25]. Critically ill patients are particularly at risk of developing these complications due to predisposing factors for TACO and TRALI, which are both linked to worse clinical outcomes [26–28].

Other risks of RBC transfusion include alloimmunization, hemolytic transfusion reactions, and septic transfusion reactions [25,29]. Transfusion-related immunomodulation (TRIM) increases a patient's susceptibility to infections and diminishes the immune response to ongoing infections [30–32]. One effective strategy to mitigate these effects is leukoreduction of RBCs, which is associated with improved clinical outcomes and a reduction in TRIM [30]. Randomized trials comparing leukoreduced to nonleukoreduced RBCs, autologous to allogeneic RBC transfusions, and restrictive to liberal RBC transfusion thresholds consistently show

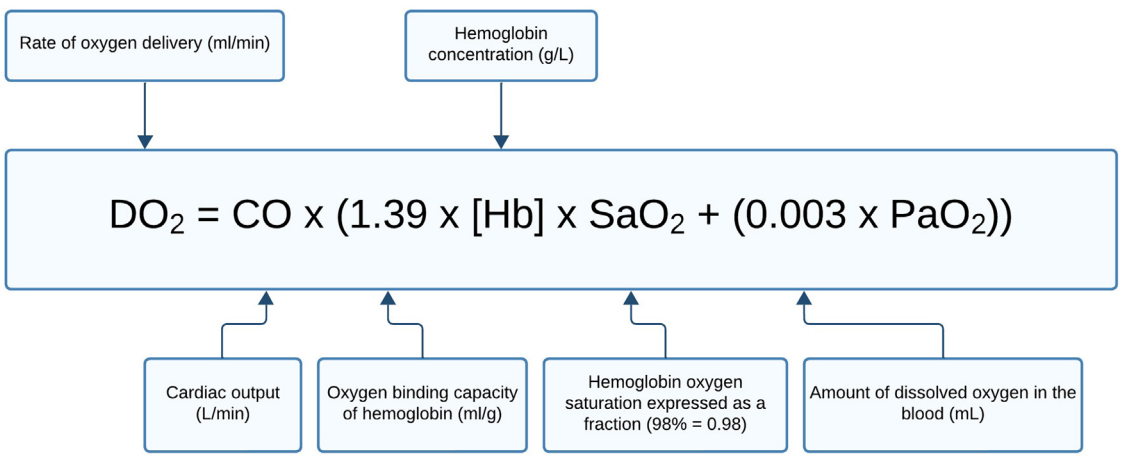
Rate of oxygen delivery (ml/min)
Hemoglobin concentration (g/L)
DO2 = CO x (1.39 x [Hb] x SaO2 + (0.003 x PaO2))
Cardiac output (L/min)
Oxygen binding capacity of hemoglobin (ml/g)
Hemoglobin oxygen saturation expressed as a fraction (98% = 0.98)
Amount of dissolved oxygen in the blood (mL)

Fig. 1. Oxygen delivery equation. Oxygen delivery (DO_2) is dependent of cardiac output (CO), hemoglobin (Hb) concentration in plasma and hemoglobin oxygen saturation (SaO_2). In patients with normal lungs SaO_2, is approximately 100%. Alterations in DO_2 are therefore mainly dependent of CO and Hb.

that patients in the leukoreduced, autologous, or restricted transfusion groups experience a lower incidence of nosocomial infections [29,30,33–35].

Moreover, there are potential long term side effects of blood transfusion which are incompletely understood. An exploratory analysis showed an association between developing spontaneous intracranial hemorrhages in recipients of blood products from donors who had a prior intracranial hemorrhage [36].

These studies show that transfusions can cause not only short-term complications but also long-term effects. Furthermore, the effectiveness of donor RBCs is lower than that of autologous RBCs, as ATP levels and 2,3-DPG (which is essential for binding to deoxyhemoglobin, the form of hemoglobin that has released oxygen, thus facilitating the release of more oxygen to tissues) remain low for an extended period [37]. Additionally, transfusions are not only associated with considerable costs but also resource scarcity as sufficient donors are required. Therefore, it would be beneficial to explore the possibility of adopting an even more restrictive transfusion policy than is currently practiced. This could result in fewer transfusions which reduces fabrication and storage costs, decreases blood donor burden and minimizes transfusion reactions.

Anemia Tolerance in Healthy Volunteers

It is now commonly accepted that it is safe to use a Hb value of 7 g/dl as transfusion trigger in nonbleeding critically ill patients. At this moment, there are no studies that have examined the effect of further lowering the Hb threshold in this population. Extrapolating from other populations, however, it appears that the Hb trigger could be safely lowered. This is most firmly supported by research on acute isovolemic hemodilution in healthy volunteers.

Weiskopf et al.[15] investigated whether an acute isovolemic reduction in Hb would lead to tissue hypoxia. The researchers rapidly decreased the Hb concentration of 21 healthy volunteers and 11 patients (prior to planned anesthesia and surgery), to a Hb concentration of 5.0 g/dL. During blood removal, isovolemia was maintained through intravenous infusion of 5% human serum albumin and/or the subject's own platelet-rich plasma. Invasive hemodynamic measurements were performed through, amongst others, employing a pulmonary artery catheter and transpulmonary thermodilution. During the experiment, arterial and central mixed venous blood was sampled to measure lactate as well as to calculate DO_2. ECG was monitored continuously from 1 hour before, through the completion of the study. A cardiac ischemic episode was based on several predefined ECG changes, however no cardiac biomarkers were measured.

The average duration of the experiment was 2.4 hours (standard deviation (SD) 0.1), with the amount of albumin and plasma infused being 1.1 times the volume of blood removed. The duration of the anemic period was not mentioned. The reduction in Hb concentration from an average of 13.1 g/dL (standard error (SE) 2.0) to 5.0 g/dL (SE 1.0) resulted in a notable decrease in systemic vascular resistance index, accompanied by increased heart rate, stroke volume index, and cardiac index – typical for a hyperdynamic circulation in response to anemia. There were no observed changes in plasma lactate concentration, and no anemia-related changes detected in ECG recordings.

The main conclusion from this study was that an acute reduction of Hb concentration to 5.0 g/dL, does not result in detectable signs of inadequate systemic oxygen transport in healthy volunteers. Neither systemic markers of inadequate oxygen transport, such as oxygen consumption and plasma lactate, nor clinical signs of hypoxemia were observed. However, this study has some limitations. First, the duration of anemia was not mentioned. Negative effects of anemia may only become apparent when sustained over a longer period, which could have been missed due to the experiment's short duration. Secondly, while electrocardiographic changes were absent, cardiac troponin levels were not measured. Troponins are highly sensitive and specific biomarkers for myocardial injury and can detect myocardial ischemia that may not be apparent on an ECG. Therefore, it is possible that there was some subclinical cardiac ischemia that was not detected by the ECG alone. Thirdly, this study was performed in healthy, resting volunteers without physical exertion, therefore these results cannot be extrapolated to critically ill patients, those with underlying (cardiac) comorbidities, or individuals with increased metabolic demands. Last, isovolemia was maintained and this is almost never the case in clinical practice where hospitalized patients are hypo- or hypervolemic due to underlying illness and/or treatment. However, this study was 1 of the first to evaluate the effect of inducing rapid isovolemic anemia in humans to as low as 5 g/dL. The minimum value of oxygen transport in humans has not been determined in this study.

Following the study from Weiskopf et al.,[15] the search for the critical level of DO_2 in anemia started with . Several studies have been published on this topic (see Table 1). Nevertheless, it is essential to acknowledge that the majority of these studies are conducted more than 2 decades ago and not within a critically ill population. There have been no recent publications to provide updated insights.

So far, none of the studies in healthy volunteers have reached critical DO_2 levels. Even with rapid hemodilution, no conclusive evidence of organ ischemia was detected. However, none of the studies recorded the duration of anemia, potentially narrowing the window to detect organ ischemia, no biomarkers for cardiac ischemia were measured and long-term effects were not assessed. The critical level of DO_2 remains unknown. It is even likely that this is organ dependent, patient dependent (e.g. comorbid atherosclerosis) and setting dependent (eg, high cardiac output states such as sepsis), but research in healthy volunteers suggests that it is possible Hb levels of less than 4.7 g/dL are tolerated without reaching a critical DO_2 level.

Anemia Tolerance in Patients

Acute Hemodilution in Patients

Healthy volunteers are not the same as patients and it is likely that patients are less able to compensate for decrease in Hb to maintain DO_2. Several studies have investigated hemodilution in patients (see Table 1).

Spahn et al.[18,19] conducted 2 studies: 1 involving patients with known coronary artery disease and chronic beta-blocker therapy, scheduled for coronary artery bypass graft (CABG) surgery, and another involving elderly patients without known cardiac disease, scheduled for major abdominal surgery. The study on patients with coronary artery disease included 90 individuals who were randomized into a hemodilution group and a control group. Exclusion criteria were a recent myocardial infarction (<10 days prior), unstable angina, valvular cardiomyopathy, left main coronary artery stenosis, rhythm other than sinus rhythm, a left bundle-branch block and Hb of less than 11 g/dL. Before and after respectively 6 and 12 ml/kg isovolemic exchange of blood hemodynamic variables, ST segment deviation and oxygen consumption were determined. Within 1 hour the Hb level decreased from 12.6 +/- 0.2 to 9.9 +/- 0.2 g/dL (mean +/- standard error of the mean (SEM), P-value $< .05$). The Hb level remained well above the current transfusion threshold for patients undergoing cardiothoracic surgery, and it is therefore no surprise that no cardiac ischemia was observed during hemodilution [6]. Hemodilution to a Hb of 9.9 g/dL was well tolerated in patients with known coronary artery disease by fully compensating the decrease in arte-

Table 1
Overview of studies performing acute isovolemic hemodilution.

	Population	Lowest Hb level reached	Volume of blood removed	Duration of experiment	Monitoring	Main outcome
Healthy volunteers						
Weiskopf et al. [15]	Healthy resting volunteers N = 32	Mean 5.0 g/dL (SE 1.0)	450-900mL	Mean 2.4 h (SD 0.1)	• Intra-arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressures • Arterial and mixed venous blood gas • ECG • Stroke volume index • Systemic vascular resistance index • DO_2 and VO_2	• Increased heart rate • Increased stroke volume index • Increased cardiac index • Decrease in systemic vascular resistance index • No changes in plasma lactate concentration • No anemia-related changes on ECG
Lieberman et al. [16]	Counscious healthy volunteers N = 8	Mean 4.8 g/dL (SD 0.2)		Mean 190 min (SD 39)	• Pulmonary artery cannula • Arterial and mixed venous blood gas • Cardiac index • Stroke volume index • Systemic vascular resistance index • DO_2 and VO_2	• Increased heart rate • Increased stroke volume index • Increased cardiac index • Decreased DO_2 • Increased VO_2 • Increased plasma lactate concentration (not exceeding normal range)
Leung et al. [17]	Conscious healthy volunteers N = 55	Mean 5.2 g/dL (SD 0.5)	Mean 8 units of blood (SD 2)	Mean 2.79 h (SD 0.74)	• Hemodynamics • Arterial oxygen content • ECG via holter	• Increased heart rate • Decreased blood pressure • Transient, reversible ST segment depression in 3 subjects at Hb level 5-7 g/dL
Patients						
Spahn et al. [18]	Elderly patients without known cardiac disease, scheduled for major abdominal surgery N = 20	Mean 8.8 g/dL (SD 0.3)	Mean 769 mL (SD 34)		• Pulse oximetry • ECG • Arterial radial catheter • Central venous catheter • Pulmonary artery catheter • Arterial and mixed venous blood gas	• Increased cardiac index exclusively due to increased stroke volume index • No increase in heartrate • Decreased mean arterial pressure • No ECG signs of myocardial ischemia
Spahn et al. [19]	Chronically B-blocked patients scheduled for elective first time CABG surgery N = 90, 60 in hemodilution group, 30 in time control group	Mean 9.9 g/dL (SD 0.2)			• Pulse oximetry • ECG • Arterial radial catheter • Central venous catheter • Pulmonary artery catheter • Arterial and mixed venous blood gas	• Increase in cardiac index • Increase in stroke volume index • No increase in heartrate • No signs of myocardial ischemia on ECG

Abbreviations: DO_2, rate of oxygen delivery; ECG, electrocardiogram; SD, standard deviation; SE, standard error; VO_2, rate of oxygen consumption.
Cardiac index, cardiac output/body surface area; Cardiac output, heart rate x stroke volume; Stroke volume index, stroke volume x body surface area.

rial Hb by increasing the cardiac index and increase of oxygen extraction. However, this study has several limitations. First, due to the extensive exclusion criteria, the included patients could be considered relatively healthy when comparing to other patients with known coronary artery disease and chronic beta blocker therapy. These patients do not resemble the severity of illness seen in critically ill patients. Additionally, it is questionable whether the results are generalizable to patients with more severe coronary artery disease. Secondly, the Hb level prior to acute hemodilution was relatively high and with a limited mean decrease of Hb 2.7 g/dL it is to be expected that no signs of hypoperfusion were found.

Patients That Refuse Blood Transfusion

Next to hemodilution studies and despite the generally accepted transfusion thresholds, there are several patient groups that regularly reach lower Hb levels as low as <4 g/dL [38–40].

The most well-described population of those refusing blood products are Jehovah's witnesses, for which multiple case reports and case series have been published describing patient related outcomes in various medical and surgical conditions (see Table 2). Within this patient population, cardiothoracic surgery appears to have similar short and long-term outcomes compared to patients who do accept RBC transfusion [41–45]. Results are similar after other surgical procedures, for example organ transplantation [46–49], liver resection and other abdominal surgery [50–52]. However, the nadir Hb level is not always mentioned and if it is mentioned, the nadir Hb is most often above 8 g/dL which is above the current transfusion threshold as well as the critical DO_2 level. Instead, authors emphasize the importance of conducting these surgeries in centers with regular transplantation procedures and experience in treating Jehovah's Witness patients.

Morbidity and Mortality

Three articles provide an overview of morbidity and mortality in patients who refuse blood transfusions for religious reasons. The authors stratified morbidity and mortality rates by Hb level (see Table 3). Carson et al. used patient data from 2 previously published studies on Jehovah's Witness patients undergoing surgery(39). The datasets included a multicenter study ($n = 12$) and a single-center study ($n = 1$), with a total of 2,083 patients. Inclusion criteria were patients aged 18 years or older in the postoperative setting, with those undergoing open heart surgery excluded. The primary outcome was in-hospital death within 30 days of surgery. Other outcomes included postoperative morbidity, defined as myocardial infarction, congestive heart failure, arrhythmia, or infection occurring within 30 days of surgery.

Of the 2083 patients, 300 (14.4%) had a postoperative Hb of 8 g/dL or less. A total of 48 patients (16.0%) died in the hospital within 30 days of surgery. The mortality rates in this study were stratified by Hb level and for each gram decrease in Hb, the unadjusted odds ratio increased by 2.4 (95% CI, 1.9-3.0). A multivariate analysis adjusting for patient age, cardiovascular disease and Acute Physiology and Chronic Health Evaluation II score (APACHE II) did not affect the odds (OR 2.5, 95% CI, 1.9-3.2).

The composite outcome of morbidity and mortality combined was only analyzed in the multicenter data since the single center data did not mention a date of the morbidity event. In this group (n = 256), 22.3% of the patients died and 74% reached a combined morbidity or mortality outcome. The most common complications were congestive heart failure, arrhythmia and pneumonia. The relationship between nadir postoperative Hb and mortality or morbidity showed a sharp increase in mortality or morbidity rates as the Hb value decreased. The unadjusted OR for each gram decrease in Hb level was 2.2 (95% CI, 1.8-2.8). When adjusting for age, cardiovascular disease and APACHE II score, the OR remained significant (OR 2.1, 95% CI, 1.7-2.6).

This renewed analysis of previously published data has some limitations. First, the data are retrospectively collected therefore an association was determined, not a causation. Furthermore, due to the retrospective nature of the study, a patient chart review, potential confounders were likely not considered. Most notably was the lack of data on the preoperative Hb. Preoperative anemia is associated with presence of anemia postoperative and mortality in various surgery subgroups including large abdominal or cardiac surgery [53–55]. Lastly, the collected data involves patients hospitalized between 1981 and 1994, well over 30 years ago. Since then, surgical procedures and perioperative care, including patient blood management, has significantly evolved.

With a similar study design, an updated study was published by Shander, et al. [38] in 2014 and the most recent by Seeber, et al. [40] in 2024. In contrast to the 2 prior studies, the latest study also included nonsurgical patients.

Seeber et al.[40] described a retrospective observational cohort study in a single center specialized in patients declining blood transfusions. The main aim was to provide a further update on mortality and composite morbidity and mortality in patients with very low Hb values who decline blood transfusion. Again, morbidity and mortality were analyzed in patients with nadir Hb levels below 8 g/dL and was stratified according to different Hb levels. Of the total 2841 patients, 159 (5.6%) had nadir Hb levels of 8 g/dL or lower and were included in the analysis. The nadir Hb levels ranged from 1.8 g/dL to 7.9 g/dL. Eighty -four patients (52.8%) were surgical patients and 75 (47.2%) were nonsurgical patients. The mean admission Hb levels were lower in the medical admissions compared to surgical admissions. In total 5 patients (3.1%) died in hospital within 30 days. There was a significant increase in the unadjusted proportion of composite morbidity and mortality events as the Hb level decreased (unadjusted OR 1.48, 95% CI, 1.05-2.09).

However, a sub-analysis of surgical patients showed, in contrast to the studies by Carson and Shander, that there was no sharp increase in mortality rates as Hb levels decreased. Furthermore, the surgical subgroup had the same mortality rate in patients with Hb levels below 6 g/dL as in those with Hb levels between 6 and 8 g/dL. These results suggest that the patients' underlying disease may have a greater impact on mortality than anemia, or that care has improved over time. Multivariable regression was not performed due to the limited sample size, which represents a significant limitation of this study. Additionally, the small number of patients with hemoglobin levels below 8 g/dL makes it challenging to draw definitive conclusions regarding mortality, as this may also be influenced by chance.

Transfusion in Extensively Burned Patients

A retrospective multicenter cohort study examined the effect of ultra-restrictive RBC transfusion (defined as a transfusion threshold <7 g/dL) vs restrictive RBC transfusion (defined a transfusion threshold 7-8 g/dL) on in-hospital mortality in patients with extensive burns (total body surface area of 50% or more) [56]. In total, 271 patients were included with 107 patients in the ultra-restrictive transfusion group and 164 patients in the restrictive transfusion group. The ultra-restrictive transfusion group was subdivided into 2 groups: <6g/dL and between 6 and 7 g/dL. No difference in in-hospital mortality was seen between the restrictive and ultra-restrictive group. However, the 32 patients in the ultra-restrictive subgroup of <6g/dL had significantly higher hospital mortality compared to the 6-7 g/dL ultra restrictive subgroup (53.1 vs 21.3%, *P*-value .001). These results suggest that a transfusion threshold below 6 g/dL in patients with extensive burns may increase the risk of mortality, although it is questionable whether they are representative of the general critically ill population [57].

In addition, this study has several limitations. As the previous studies, this was a retrospective study with risk of confounding and only suitable to establish associations but not causality. Additionally, the study was conducted in 3 hospitals in Eastern China, which limits the generalizability of the findings to other populations or regions. To mitigate the impact of potential confounders and selection bias, propensity score matching was utilized to balance baseline characteristics between the ultra-restrictive and restrictive transfusion groups. However, this approach was not applied to the subgroups within the ultra-restrictive cohort due to the small sample size.

Acute Anemia in Hematology Patients

Another patient group in which lower Hb levels are sometimes accepted, are patients diagnosed with hematological con-

Table 2
Patients who refuse blood transfusion (Jehovah's Witnesses), stratified by type of surgery.

		Study design	N	Hb prior surgery in g/dL, mean (SD)	Intraoperative Hb in g/dL, mean (SD)	Hb after surgery in g/dL, mean (SD)	Outcome
Cardiothoracic surgery							
	Bhaskar et al. [41]		49	13.7 (1.7)		10.8 (1.5)	• Significantly less bleeding and no differences in adjusted and unadjusted operative mortality (P-value 0.51, 95% CI, 0.12-3.50) or ICU and postoperative length of stay (P-value 0.60, 95% CI, 0.45-3.99) between patients who refused blood products vs controls
	Moraca et al. [42]		40	14.1 (1.6)			• Patients were classified as high risk (45%, $n = 18$) and low risk (55%, $n = 22$) with an overall 30-day mortality of 5% ($n = 2$, both deaths occurring in the high-risk group).
	McCartney et al. [43]	Retrospective single center	45	14.0 (1.1)	10.3 (2.2)	10.6 (1.3)[a] 9.9 (1.8)[b]	• 90-day mortality of 0%
	Willcox et al. [44]	Retrospective propensity-matched multicenter	118	8.9 (1.5)[c]			• Acute kidney injury was lower in patients refusing transfusion (8% vs 22%, P-value 0.003)Patients refusing transfusion had lower postoperative blood loss (P-value 0.02) and shorter postoperative length of stay (P-value <0.001)No difference in morbidity (P-value 0.46) or mortality (P-value 0.68)
	Nanni et al. [45]	Case control study	113	14.1 (1.5)		10.8 (1.8)[d] 10.6 (1.6)[e]	• No difference in hospital mortality in Jehovah's Witnesses vs controls (2.7% vs 1.8%, P-value 1.00) • Mortality was high (40%) in Jehovah's Witnesses patients with postop Hb <8 g/dL • Jehovah's Witnesses did not have a higher occurrence of the composite outcome (adjusted odds ratio 0.91, 95% CI 0.54-1.57) defined as a composite of in-hospital perioperative adverse events and in-hospital mortality vs controls • Jehovah's Witnesses did not have a higher all-cause mortality (adjusted hazard ratio 0.77, 95% CI 0.24-2.42) vs controls
Organ transplantation							
Heart	Sander et al. [46]	Case control study	8	13.0 (2.0)[f]			• There was no difference in short or long-term outcomes between Jehovah's Witnesses and controls
Liver	Costanzo et al. [47]	Retrospective single center	13	14.5 (1.9)		10.5 (2.1)[g] 12.4 (2.0)[h]	• Of the 13 recipients, 12 were alive at 1 year follow-up, 1 died due to septic complications • Liver transplantation in selected Jehovah's Witnesses patients can be feasible and safe provided that it is carried out at a very experienced center with multidisciplinary approach prior and postsurgery
Kidney and pancreas	Boggi et al. [48]		6	11.7 (1.1)[i]		9.9 (0.7)[h]	• All patients were alive and well after mean follow-up period of 31.4 months

(*continued on next page*)

Table 2 (*continued*)

		Study design	N	Hb prior surgery in g/dL, mean (SD)	Intraoperative Hb in g/dL, mean (SD)	Hb after surgery in g/dL, mean (SD)	Outcome
Kidney	Carvalho et al. [49]	Retrospective single center	143 (10 pediatric)				• There was no difference in incidence of clinical indication for transfusion (13.3 vs 11.3%, P-value 0.640) of Jehovah's witness vs controls • No difference in the proportion of patients showing a decrease of >2 g/dL Hb during the first week after transplantation or hemorrhagic complications in Jehovah's witness vs controls
Liver resection and other abdominal surgery							
	Kulkarni et al. [50]	Retrospective single center	100	13.4 (3.1)[j] 13.2 (3.0)[k]		11.4 (4.3)[j] 10.3 (3.7)[k]	• In the liver resection cohort, morbidity and mortality rates were 17.5% and 0% respectively. These compare favorably to previously reported morbidity and mortality rates in transfusion-eligible patientsPancreas surgery showed the same trend with comparable morbidity and mortality rates
	Lim et al. [51]	Retrospective single center	10	13.4[l]		12.6[l]	• Two patients had major complications • The risk/benefit ratio of elective liver resection was maintained in selected adult Jehovah's Witness patients by using a variety of blood conservation techniques

SD, standard deviation.
[a] In patients who received postoperative erythropoietin stimulating agent(s).
[b] In patients who did not received postoperative erythropoietin stimulating agent(s).
[c] Minimum Hb level.
[d] 48-72 h after surgery.
[e] 72-96 h after surgery.
[f] at referral.
[g] end of surgery.
[h] Discharge home.
[i] at admission.
[j] Liver resection group.
[k] Pancreas resection group.
[l] no SD mentioned.

Table 3
Mortality and morbidity in patients who refuse blood transfusion, stratified by nadir Hb level in g/dL

Nadir Hb level (g/d)	Total study population, N	30-day in hospital mortality, N (%)	Composite morbidity and mortality, N (%)
Carson et al. [39]			
≤4.0	59	27 (45.8)	25 (71.4)
4.1-5.0	32	11 (34.4)	15 (57.7)
5.1-6.0	54	5 (9.3)	14 (28.6)
6.1-7.0	56	5 (8.9)	11 (22.0)
7.1-8.0	99	0 (0.0)	9 (9.4)
Overall	300	48 (16.0)	74 (28.9)
Shander et al. [38]			
≤4.0	22	6 (27.6)	13 (59.1)
4.1-5.0	31	6 (19.4)	13 (41.9)
5.1-6.0	49	7 (14.3)	20 (40.8)
6.1-7.0	58	3 (5.2)	12 (20.7)
7.1-8.0	133	2 (1.5)	31 (23.3)
Overall	293	24 (8.2)	89 (30.4)
Seeber et al. [40]			
≤4.0	2	1 (50.0)	1 (50.0)
4.1-5.0	6	0 (0.0)	4 (66.7)
5.1-6.0	12	0 (0.0)	3 (35.0)
6.1-7.0	22	1 (4.5)	7 (31.8)
7.1-8.0	42	2 (4.8)	4 (9.5)
Overall	84	4 (4.8)	19 (22.6)

Morbidity is defined as acute myocardial infarction, cardiac failure, (deep) wound infection, arrhythmia and pneumonia.

Table 4
Transfusion strategy in patients with hematologic condition

	Hematologic condition	Advised transfusion strategy
Acute anemia	Auto-immuun hemolytic anemia	Minimize use of transfusion[a] Absolute transfusion threshold <6 g/dL[b]
	Acute aplastic anemia	Considering transfusion <7 g/dL[c] Absolute transfusion threshold <6 g/dL[d]

[a] Jäger et al. [58].
[b] Mulder et al. [59].
[c] Killick et al. [63].
[d] Hochsmann et al. [64].

ditions. These patients can be divided into those with chronic anemia such as patients with hemoglobinopathies (for example thalassemia and sickle cell disease) or acute anemia as a result of auto immune hemolytic anemia (AIHA) or acute aplastic anemia.

Table 4 provides an overview of advised transfusion strategy in hematology patients with acute anemia. Overall, all transfusion strategies are based on expert opinion and very limited evidence is available. Below, we will discuss AIHA and aplastic anemia in more detail as examples of conditions in which a Hb <7.0 g/dL is well tolerated.

Auto-Immune Hemolytic Anemia

AIHA is a condition that typically presents acutely. Autoantibodies result in the destruction of donor RBCs [58]. There is no consensus on a specific transfusion trigger in these patients. It is advised to minimize the use of transfusions in a patient-specific approach [58,59], and transfuse only for vital indications such as severe anemia (defined <6 g/dL and/or presence of cardiovascular risk factors or hypoxemia symptoms) [59].

Depending on the severity of AIHA, admission to the ICU may be necessary. Results from a large French observational study of 62 patients with AIHA admitted to the ICU specifically for AIHA management showed that the mean Hb level at admission was 4.3 g/dL, with half of the patients presenting with at least 1 failing organ at the time of admission. Eight (12.9%) patients died in the ICU. Causes of death were hypoxic cardiac arrest due to refractory AIHA in 5 (62.5%) patients and massive pulmonary embolism in 3 (37.5%) patients. When comparing the characteristics of ICU AIHA patients with AIHA patients not admitted to the ICU (N = 138), a univariate analysis showed several factors associated with ICU admission. Laboratory values included low Hb level (defined as below 6 g/dL), low reticulocyte count (defined as $<100 \times 10^9$/L), high leukocyte count, and a high indirect bilirubin level at diagnosis. Other factors were young age and presence of the auto-immune Evans syndrome [60]. This study did not describe patient outcomes or the development of organ ischemia of AIHA patients not admitted to the ICU.

Another French retrospective study included 44 patients with AIHA admitted to the ICU. Twenty-one patients were admitted because of direct consequences of AIHA due to profound anemia without organ dysfunction (N = 19), post-RBC transfusion acute respiratory failure (N = 2) and 1 patient for myocardial infarction. The median Hb level at admission was 6.8 g/dL (Inter Quartile Range (IQR) 4.6-9.1) with troponin level elevated in 2 patients (5%). Thirteen patients (30%) died in the ICU with organ ischemia in 5 patients (39%) being the cause of death. Unfortunately patient outcomes or the development of organ ischemia was not compared between patients with AIHA being the primary cause of ICU admission and AIHA patients who were admitted to the ICU due to different reasons [61].

Aplastic Anemia

The individualized approach to transfusion decisions is also applied to patients with acute aplastic anemia in which loss of hematopoietic stem cells results in anemia. This condition can arise due to autoimmune mechanisms, drugs (cytotoxic chemotherapy), viral infections (hepatitis, HIV, parvo B19), or clonal and genetic disorders. Patients most commonly die of infection due to neutropenia after hematopoietic cell transplantation (HCT) and/or immunosuppressive therapy although bleeding due to thrombocytopenia is also a common cause of death. Supportive therapy is often necessary, typically involving multiple blood transfusions [62]. Generally, a restrictive transfusion policy is pursued, with a transfusion threshold of 7 g/dL, while even lower is often accepted since these patients require transfusion so often. The decision for transfusion is based on clinical symptoms (signs of hypoxic anemia; signs of hemorrhage) with quality of life playing an important role [63]. However to avoid hypoxic cell damage, Hb levels of 6.0 g/dL or lower are considered to be an absolute transfusion threshold although this is based on very limited evidence [64]. A higher number of pre-HCT RBC transfusions is associated with increased transplant-related mortality and decreased overall survival [65].

Future Perspectives

Future studies could focus on further exploring Hb reduction in a controlled setting, with critically ill patients being particularly well-suited for this. The ICU provides high-level, 24-hour care and employs continuous, invasive monitoring to detect and address symptoms of anemia early.

A feasibility study is currently underway at Amsterdam UMC to assess whether an ultra-restrictive transfusion policy (5 g/dL) is viable compared to the current threshold (7 g/dL). This study is undergoing the IRB approval process. Positive results from this feasibility study could pave the way for a large, multicenter, randomized controlled trial.

Additionally, other studies suggest that patient related outcomes may not be solely influenced by the nadir hemoglobin level. Instead, the change in Hb levels (delta Hb) could be a more accurate predictor for adverse outcomes . A study from Spolverato et al.,[66] showed that a delta Hb level of 50% or greater following gastrointestinal surgery was associated with complications, especially ischemic adverse events. A greater percentage change in delta Hb was also independently associated with a higher risk of perioperative complications and hospital-related infections in patients undergoing spine surgery [67]. While there is confounding by indication (greater delta Hb could mean more complications), delta Hb may address the issue of organ compensation and tolerability of anemia.

However, as mentioned in the introduction, it is important to recognize that Hb levels have a limited correlation with actual oxygen delivery insufficiency DO_2 [24]. Hb is a derived value mea-

sured in venous or arterial blood, which does not necessarily reflect hemoglobin levels at the capillary level or within the microcirculation [68,69]. The microcirculation can be directly observed at the bedside using handheld vital microscopes, which can be applied to areas such as the sublingual region [70]. However, the effects of RBC transfusion on sublingual microcirculation in critically ill patients showed varying results depending on the patient population [71]. While RBC transfusion can improve microcirculatory parameters in certain patient groups, such as intraoperative [72–75] and anemic hematologic patients [76], it did not have the same positive effects in septic patients [71,77–80]. The clinical application of bedside handheld vital microscopes still faces several challenges [70].

Alternative triggers for RBC transfusion, as opposed to relying solely on hemoglobin levels, could focus more on the physiological effects of hemoglobin reduction such as on SvO2 or oxygen extraction ratio with therefore applying a more individualized approach to patient care. Currently, a multicenter international trial is underway to evaluate the impact of an oxygen extraction-guided transfusion strategy in critically ill patients to demonstrate the potential advantages of employing an individualized transfusion strategy compared to a standard restrictive approach defined as 7 g/dL [81].

Lastly, the question arises as to whether there are alternative treatments for anemia in the ICU population. Options may include the use of iron, erythropoietin (EPO), or a combination of both. The European Society of Intensive Care Medicine (ESICM) has developed guidelines on transfusion strategies for nonbleeding critically ill adults with anemia [11].

While there is some indication that EPO may reduce mortality, this effect seems to be predominantly observed in trauma patients, with no such benefit in the nontrauma population [82,83] . If true, the reduction in mortality among trauma patients does not appear to be driven by the erythrogenic effects of EPO (ie, increased red blood cell production), as the decrease in transfusions was mainly seen in the nontrauma group [82,84,85]. However, subsequent large RCTs have failed to confirm this outcome in trauma patients, raising doubts about the validity of these earlier findings [86].

Regarding iron supplementation**,** ESICM guidelines advise against its use in critically ill patients with anemia due to the lack of a clinically significant reduction in transfusions based on the pooled results of 6 RCTs [87–92]. The financial costs and logistical burden of administering iron to all critically ill patients, without clear clinical benefits, were also deemed considerable. For patients who refuse blood transfusions, consideration may be given to iron supplementation or the administration of EPO [11].

Conclusion

The transfusion threshold of 7 g/dL is currently the standard of practice in critically ill patients and is considered safe even in most high-risk patient categories. Research involving acute hemodilution has not identified a critical Hb level resulting in an impaired DO_2 in healthy volunteers nor patients. In current clinical practice, there are several patient groups in which a Hb level lower than 7 g/dL is applied and well tolerated. Individualized patient care strategies seem to be successful in these cases. Taken together, these findings suggest that there may be potential to further lower the transfusion threshold.

Author Contributions

CS drafted the manuscript. RK and ALP contributed to writing and provided critical feedback. APJV and MCAM supervised the project and reviewed the manuscript, providing essential revisions. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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